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Bone and Mineral Metabolism

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Disclosures

- I have nothing to disclose

Outline

- Minerals – Homeostasis and Disorders

- Hormones

- PTH
 - Vitamin D
 - FGF 23

- Organs

- Intestine
 - Kidney
 - Bone

- Bone – Physiology and Disorders

	Content Categories	Initial Certification and In-Training	Maintenance of Certification (MOC)
1.	Carbohydrate Metabolism	16%	16%
2.	Bone and Mineral Metabolism	8%	8%
3.	Thyroid Hormones (Thyroxine [T4] and Triiodothyronine [T3])	13%	14%
4.	Adrenal Disorders	12%	12%
5.	Pituitary/Hypothalamus	10%	10%
6.	Growth	12%	14%
7.	Reproductive Endocrine System	12%	12%
8.	Other Hormones	3%	3%
9.	Lipoproteins and Lipids	3%	3%
10.	Multiple endocrine neoplasia and polyglandular autoimmune disease	2%	2%
11.	Methods and Biological Principles	4%	2%
12.	Core Knowledge in Scholarly Activities	5%	4%

New outline 5%



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Mineral Homeostasis



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Minerals – Calcium

- Structural role in hard tissues (bone and teeth); important regulatory role in metabolic and signaling pathways
- In circulation: 50% ionized; 50% bound to albumin and other anions
- Serum albumin levels
 - \downarrow 1 mg/dL Albumin = \downarrow 0.8 mg/dL Ca, normal iCa level
- Serum pH (pH 7.4 = 1.15-1.35 mmol/L iCa)
 - Alka**LO**sis (high pH): **LOW** iCa



Minerals – Phosphate

- Structural role in hard tissues (bone, teeth)
- Key intracellular component and cofactor in signaling pathways
 - Phosphorylation of proteins, lipids, ATP, backbone of nucleic acid
- In blood:
 - 84% ionized (phosphoric acid or inorganic phosphate),
 - 10% protein bound, 6% complexed with cations
- Soft tissues contain 10-fold more phosphate than calcium

Age	mg/dl	mmol/L
0-9 days	4.5-9	1.45-2.91
10 days to 2 years	4-6.5	1.29-2.1
3-9 years	3.2-5.8	1.03-1.87
10-15 years	3.3-5.4	1.07-1.74
>15 years	2.4-4.4	0.78-1.42

Harriet Lane



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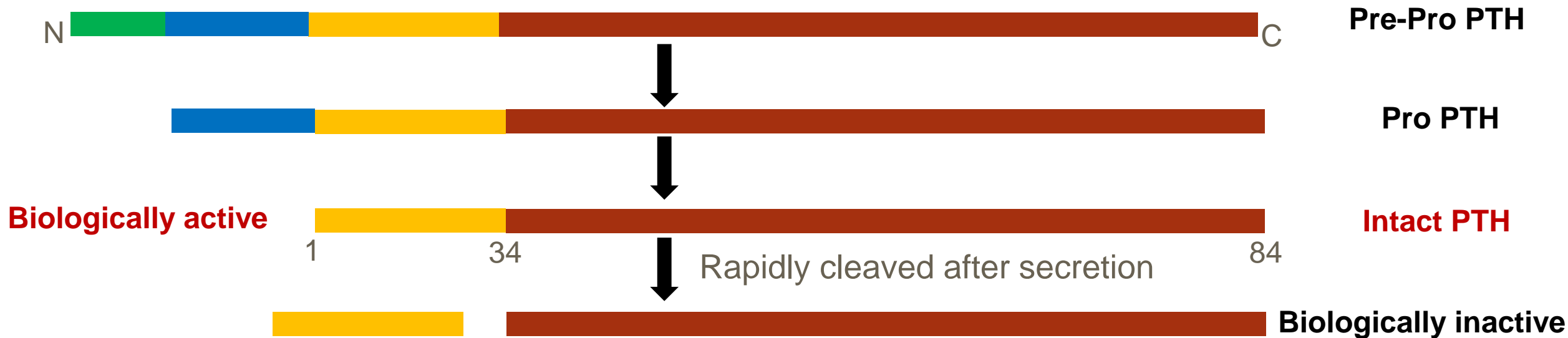
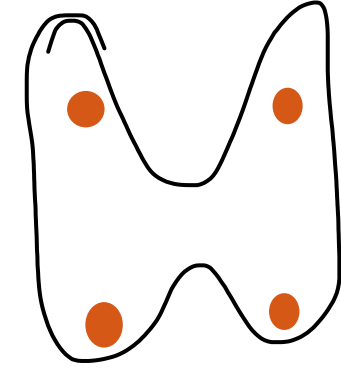
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Minerals - Magnesium

- Most intracellular – bone, muscle, soft tissue
- Bound to ATP, nucleotides, enzyme complexes, crucial for enzymatic reactions
- Important for PTH secretion and action
 - **Hypermagnesemia suppresses PTH secretion

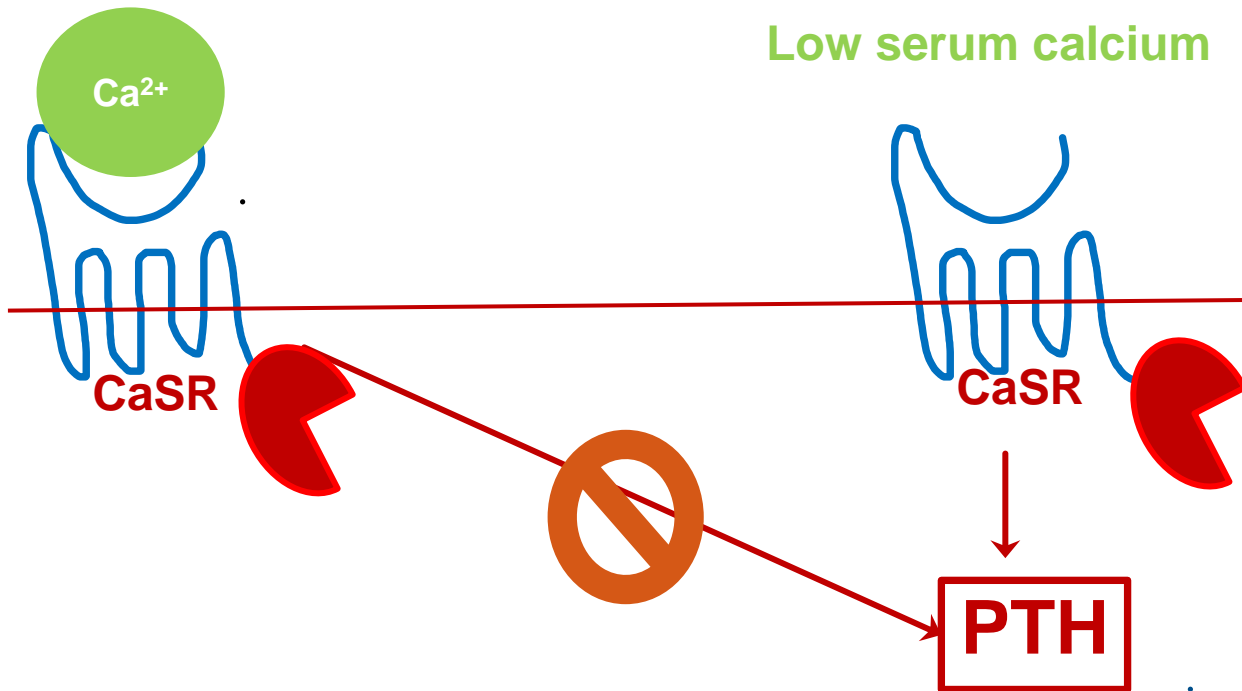
Parathyroid Hormone (PTH)

- Endodermal lining of 3rd and 4th pharyngeal pouches
- Principal (chief) cells secrete PTH
- 84 amino acid polypeptide; short $t_{1/2} < 5$ minutes

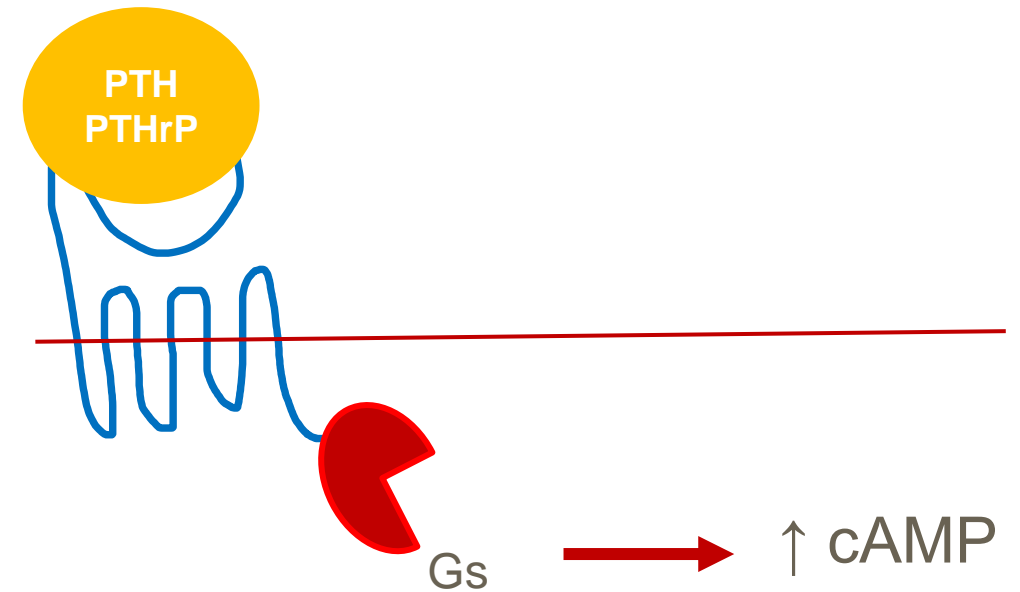


Receptor and Signaling

Calcium Sensing Receptor (CaSR)

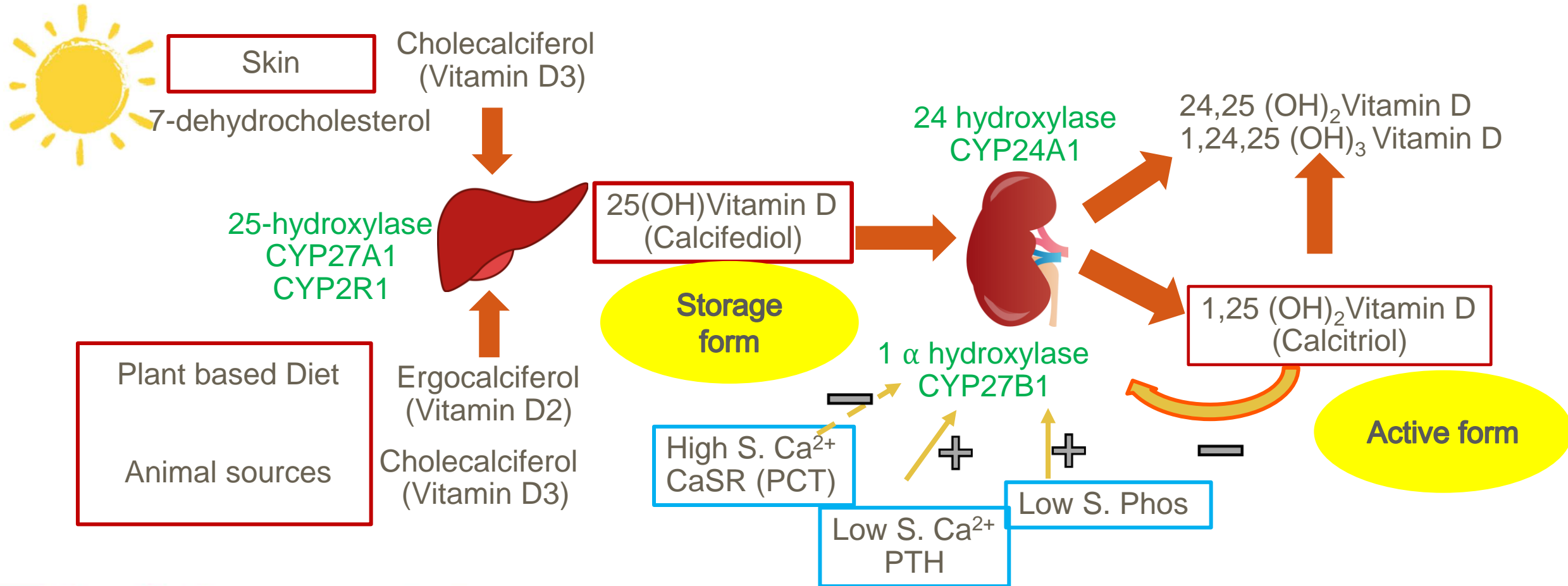


PTH/PTHrP Receptor



Measurement of plasma and urinary cAMP
is a measure of PTH activity

Vitamin D



Vitamin D Receptor (VDR)

- Nuclear hormone receptor
- Regulates gene expression in target tissues
 - Small Intestine: increases calcium channels and calbindin etc.
 - Bone: sensitizes osteoblasts to PTH
regulates osteoid production and calcification
 - Kidney: promotes phos reabsorption by PCT (NaPi cotransporters)
 - Parathyroid gland: inhibit PTH gene expression
stimulate CaSR gene expression

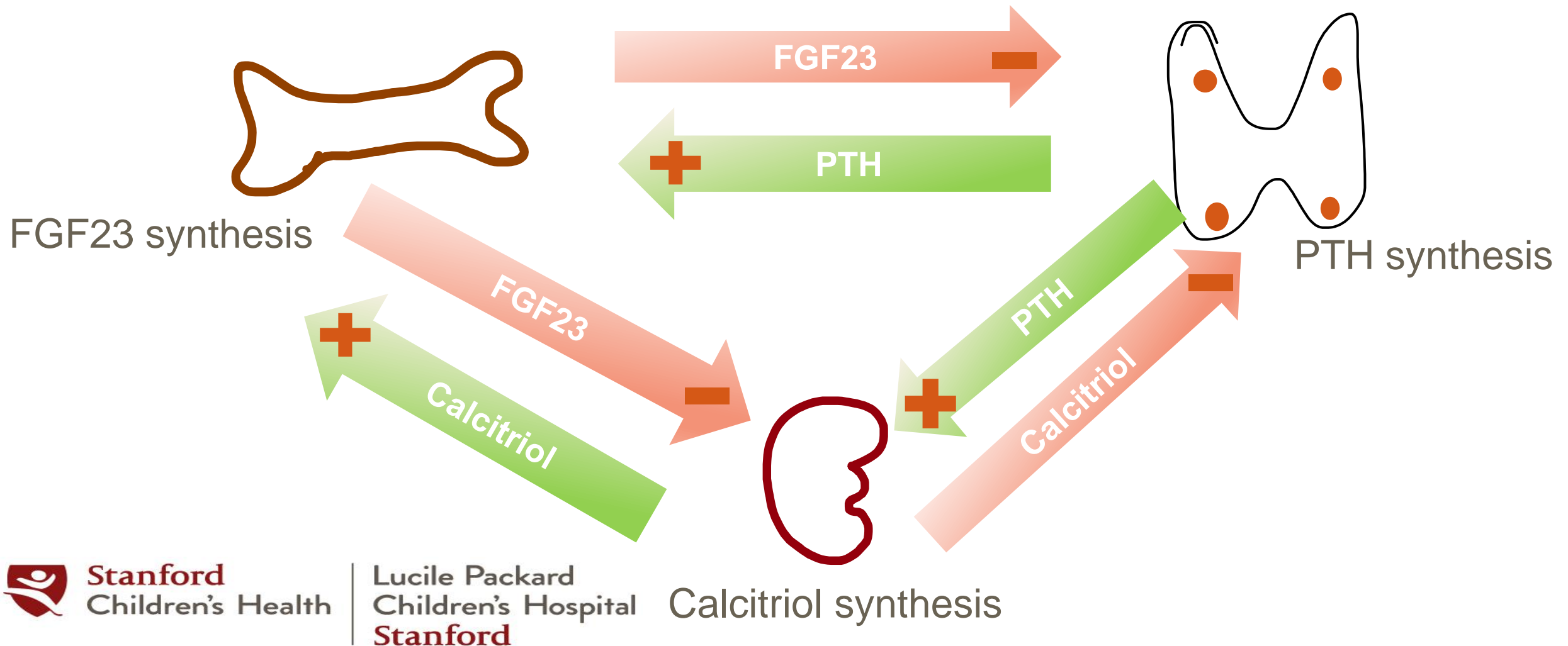


Fibroblast Growth Factor 23 (FGF23)

- Glycoprotein produced from bone (osteocytes)
- Intact FGF23 is biologically active
 - Cleaved by proteases into N & C terminal fragments (inactive)
- Regulation:
 - Upregulated by ↑ S. Phosphorus and calcitriol
 - Downregulated by PHEX, DMP -1 (by unknown mechanism)
- FGF Receptor (tyrosine kinase receptor) and co-receptor Klotho
 - Promotes phosphorus excretion by kidneys (Degradation of NaPi cotransporter)
 - ↓ Calcitriol level



Cross Talk between hormones



- Calcium: duodenum and jejunum
 - **Active** (transcellular; epithelial calcium channels TrpV)
 - Passive (paracellular)
 - Dietary sources: dairy products
- Phosphorus: jejunum
 - **Passive** (paracellular)
 - Active (transcellular; NaPi cotransporter)
 - Abundant in western diet
- Magnesium: Passive and active (TRPM 6 channel) absorption
- Calcitriol increases Ca^{2+} absorption and marginally increases PO_4 absorption
- PTH does not have a direct effect, but indirectly via activating 1α hydroxylase



- **Calcium:**
 - 10 g filtered
 - 200 mg/day loss in urine
 - PCT - passive, paracellular
 - **DCT** - transcellular reabsorption stimulated by PTH

Thiazides: ↓ calcium excretion

Furosemide and Corticosteroids:
↑ calcium excretion

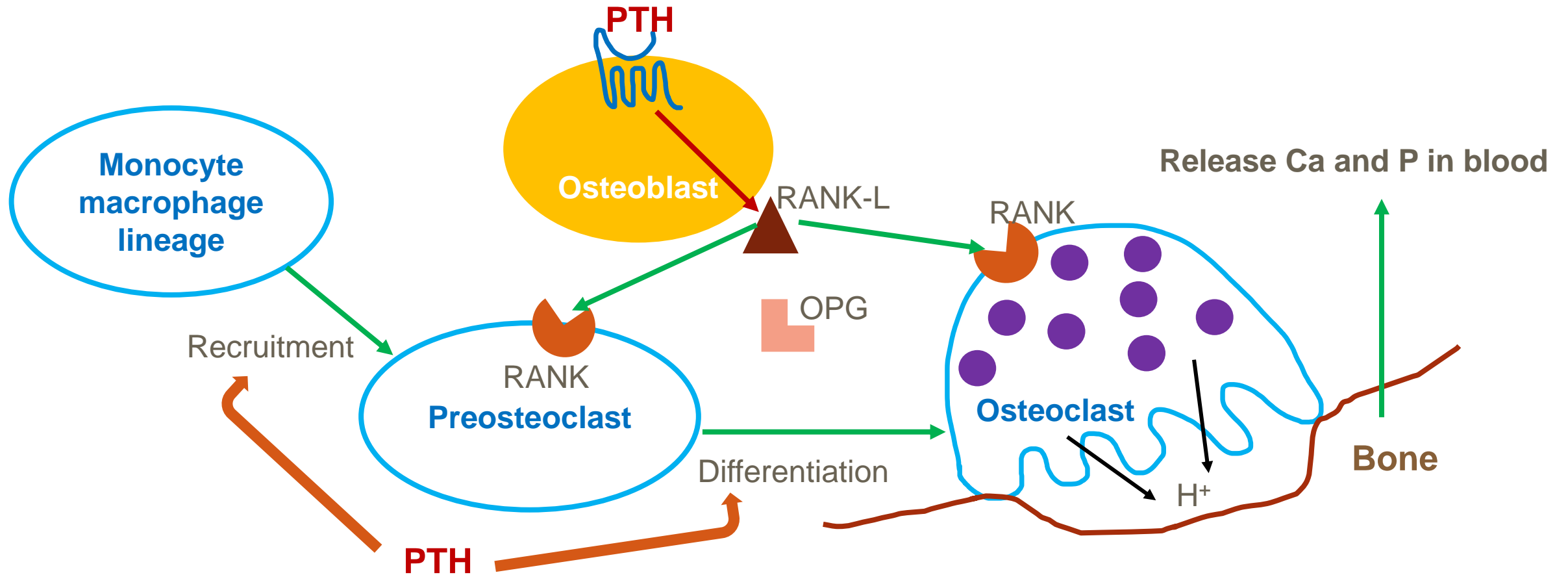
- **Phosphorus:**
 - Most reabsorbed by **PCT** (active transcellular; NaPi cotransporter)
 - downregulated by PTH, FGF23
 - upregulated by 1,25 (OH)₂ Vitamin D
 - **Magnesium:**
 - During magnesium depletion, kidney conserves magnesium
 - During hypermagnesemia, kidney losses increase likely via CaSR
- PTH increase magnesium reabsorption**



Bone



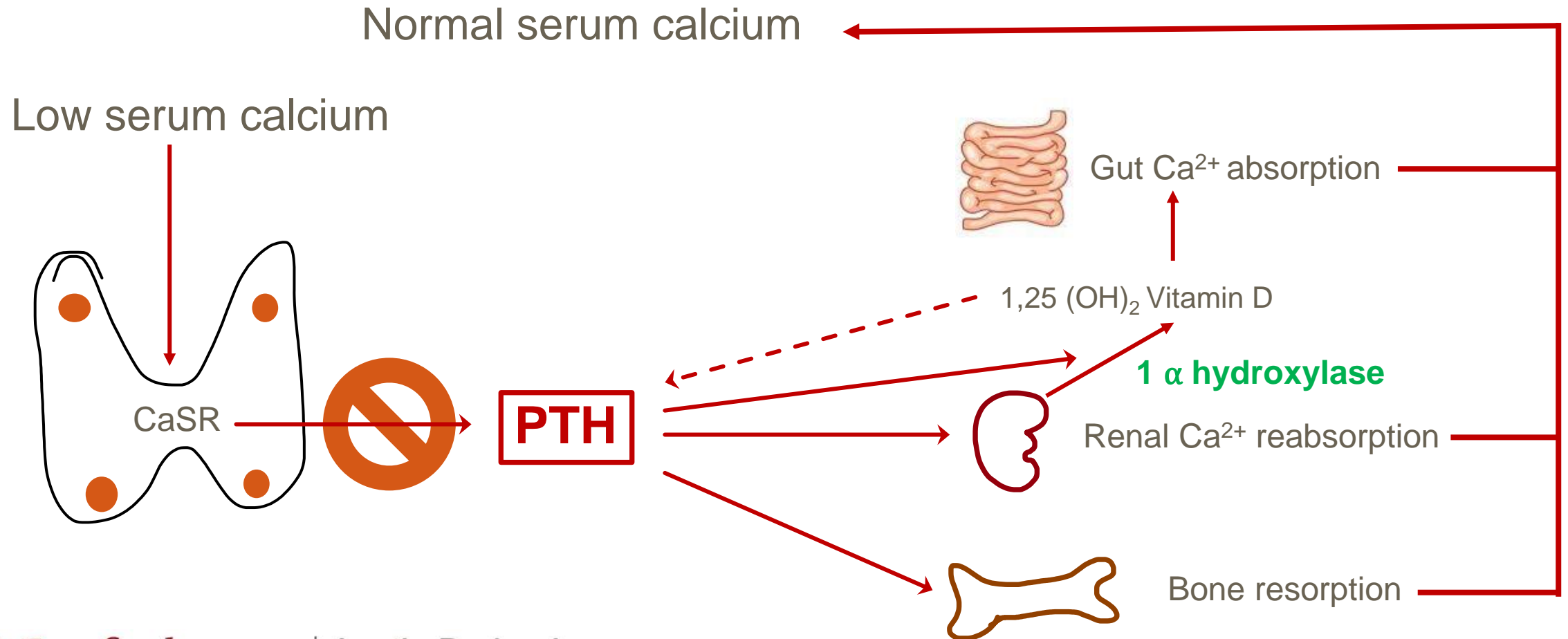
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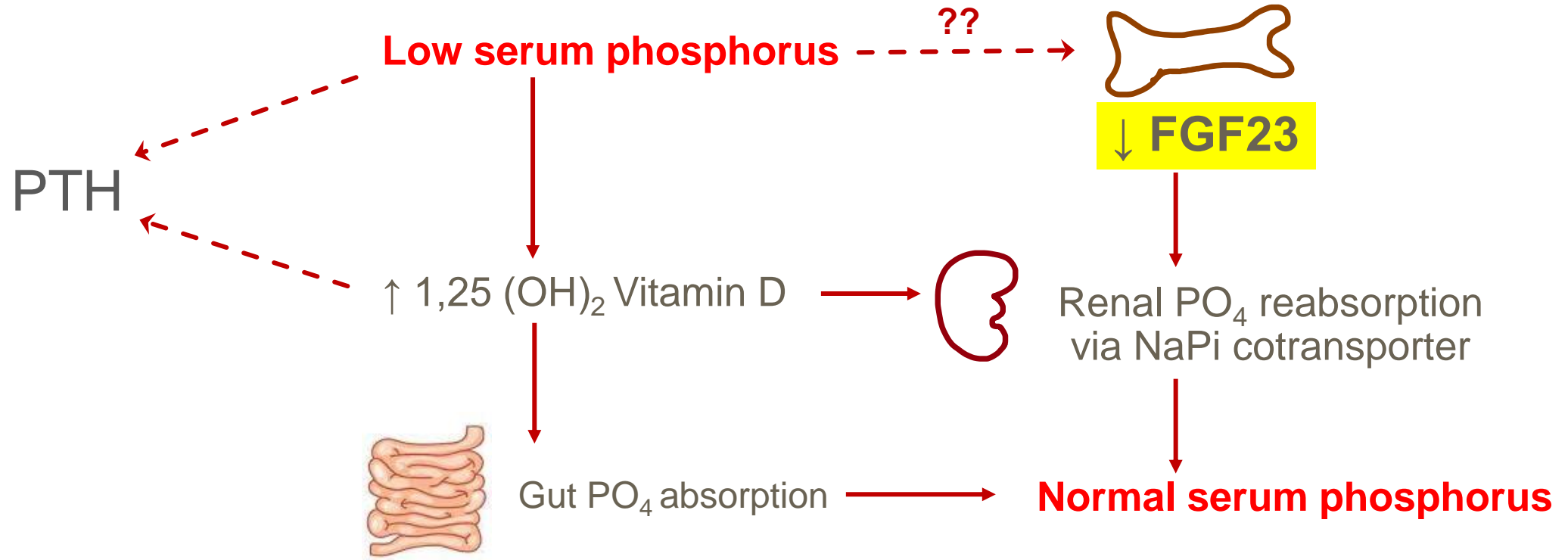
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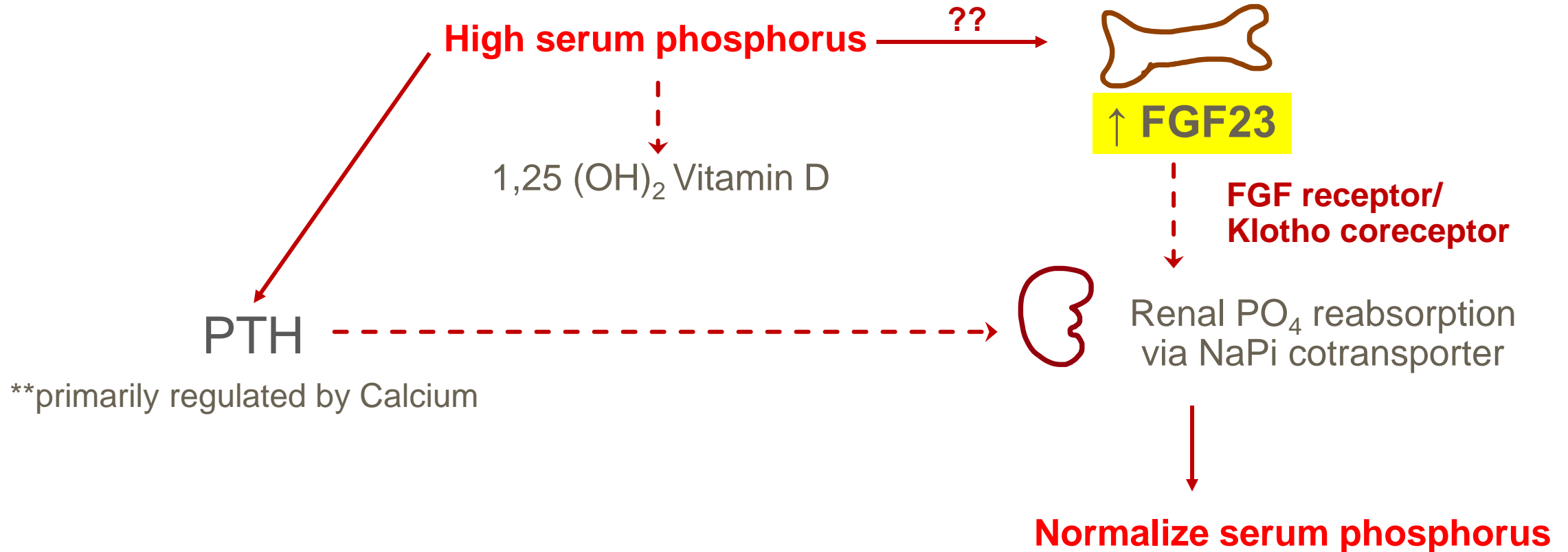
Calcium Regulation



Phosphate Regulation



Phosphate Regulation





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Disorders of Mineral Metabolism



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Hypocalcemia



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Hypocalcemia

- Symptoms:
 - Irritability
 - Muscle twitches
 - Jitteriness
 - Tremors
 - Poor feeding
 - Lethargy
 - Seizures
- Signs:
 - Trousseau's sign
 - Chvostek's sign



Hypocalcemia - Causes

Neonatal

- **Early-Onset (0-72 hours)**
 - IDM, IUGR, birth asphyxia, prematurity
 - Maternal hypercalcemia
 - Hypoparathyroidism (transient or permanent)
- **Late-Onset (>72 hours)**
 - High phosphorus intake
 - Low magnesium
 - Maternal vitamin D deficiency
 - Hypoparathyroidism

Childhood

- Congenital Hypoparathyroidism
- Acquired hypoparathyroidism
 - surgery, trauma, autoimmune, radiation, infiltration
- Pseudohypoparathyroidism
- Nutritional deficiency
 - calcium or vitamin D
- Hypomagnesemia
 - Chronic diarrhea, malnutrition, Bartter syndrome
- Renal insufficiency
- Acute hyperphosphatemia

Congenital Hypoparathyroidism

- Labs:
 - ↓ Ca, ↑ Phos, ↓ PTH, normal 25(OH)Vitamin D, **low** 1,25 (OH)₂ Vitamin D, ↓ urine Ca**
- Causes:
 - Syndromes:
 - DiGeorge syndrome (most common cause in pediatrics)
 - CHARGE , HDR syndrome (Barakat syndrome), Sanjad-Sakati or Kenny-Caffey syndrome
 - Autosomal dominant and Autosomal recessive (production of PTH)
 - X linked recessive (development of parathyroid gland)
 - Activating mutation (AD) or antibody mediated stimulation of CaSR in parathyroid gland
 - Mitochondrial disorders (eg, MELAS syndrome, Kearns-Sayre syndrome)
- Physical findings:
 - Ectopic (intracranial- basal ganglia) calcifications



Pseudohypoparathyroidism (PHP)

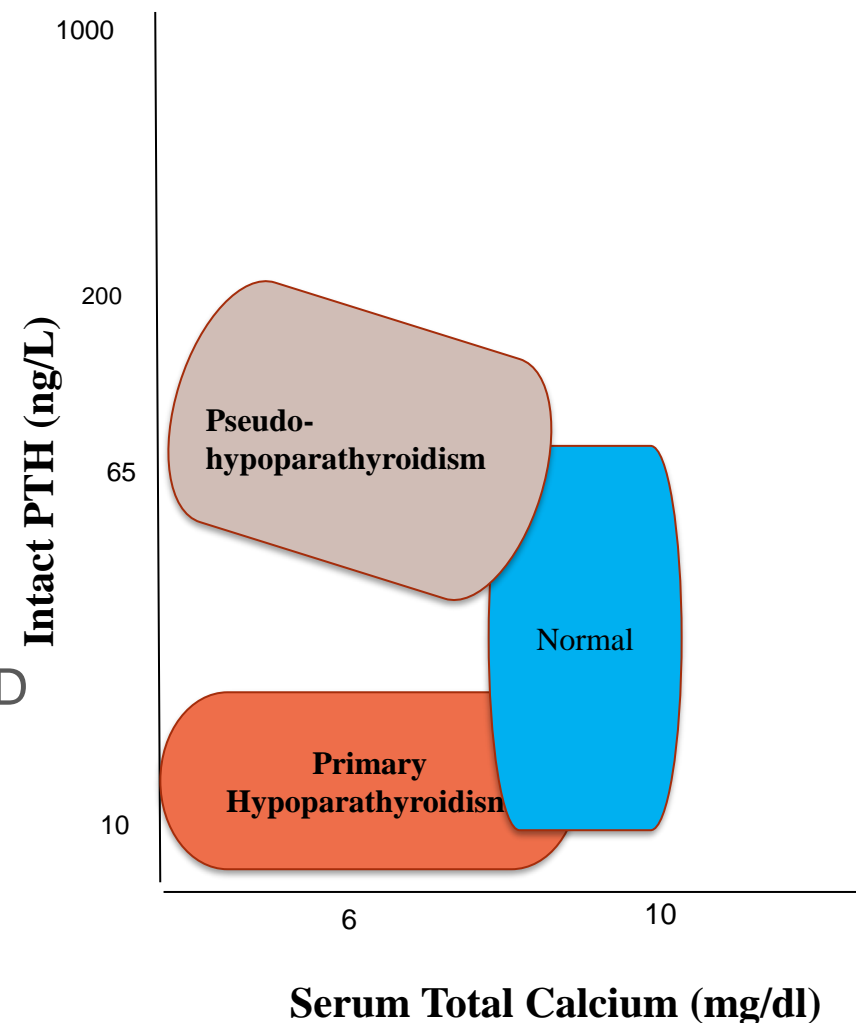
- Labs:
 - ↓ Ca, ↑ Phos, ↑ PTH, normal 25(OH)Vitamin D, low-normal 1,25(OH)₂ Vitamin D
- PTH signaling is impaired; imprinting defect
 - Target tissue resistance in PCT (kidneys) -> hyperphosphatemia and low calcitriol
 - No resistance in DCT (kidneys) -> hence no hypercalciuria (unless over treated)
 - Variable resistance in bone -> ? skeletal fragility, low BMD vs high BMD
- Albright Hereditary Osteodystrophy (AHO):
 - Round facies, obesity, brachydactyly, short stature, developmental delay, dental hypoplasia, subcutaneous calcifications
 - **Pseudo**-pseudohypoparathyroidism (PPHP): AHO alone, no lab abnormalities



	PHP IA	PHP IB	PHP IC	PHP type II	Pseudo PHP
Gsα mutation	Maternal inheritance	Sporadic or maternally inherited or Methylation defect	None	None	Paternal inheritance
AHO phenotype	+	-	+	-	+
PTH resistance (↓Ca, ↑Phos, ↑PTH)	+	+	+	+	-
Other Hormone (TSH, LH/FSH, GHRH) resistance	+	+(TSH)	+	-	-
Renal cAMP production to PTH	↓	↓	normal	normal	normal
Phosphaturic response to PTH	↓	↓	↓	↓	normal

Hypocalcemia- Evaluation

- Review of maternal, gestational, birth and family Hx
- Laboratory evaluation – the **critical labs!**
 - Total calcium/albumin, or iCa^{2+}
 - Serum Phosphorus
 - Serum Magnesium
 - Serum Creatinine
 - iPTH (at the time of low calcium)
 - Spot or 24-hour urine Ca/Cr
 - Alkaline phosphatase
 - 25 (OH) vitamin D
 - 1,25 (OH)₂ vitamin D
- Maternal labs – calcium, phosphorus, iPTH, 25 (OH) vitamin D
- Genetic studies

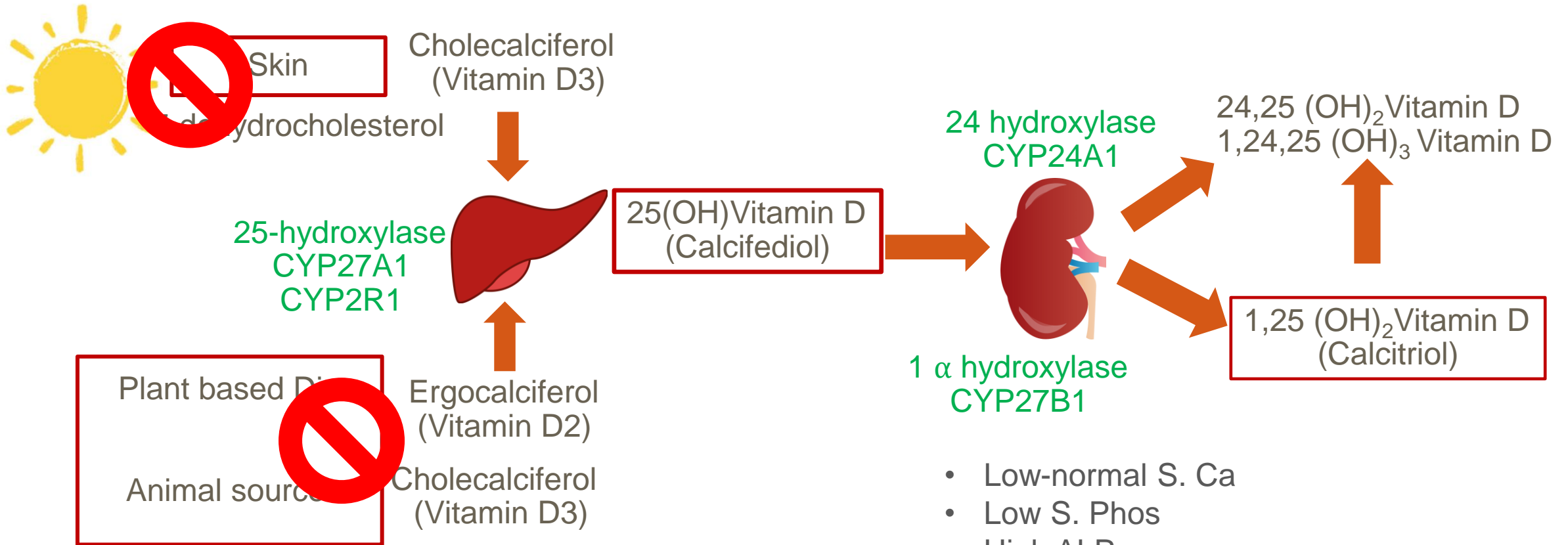


Hypocalcemia - Management

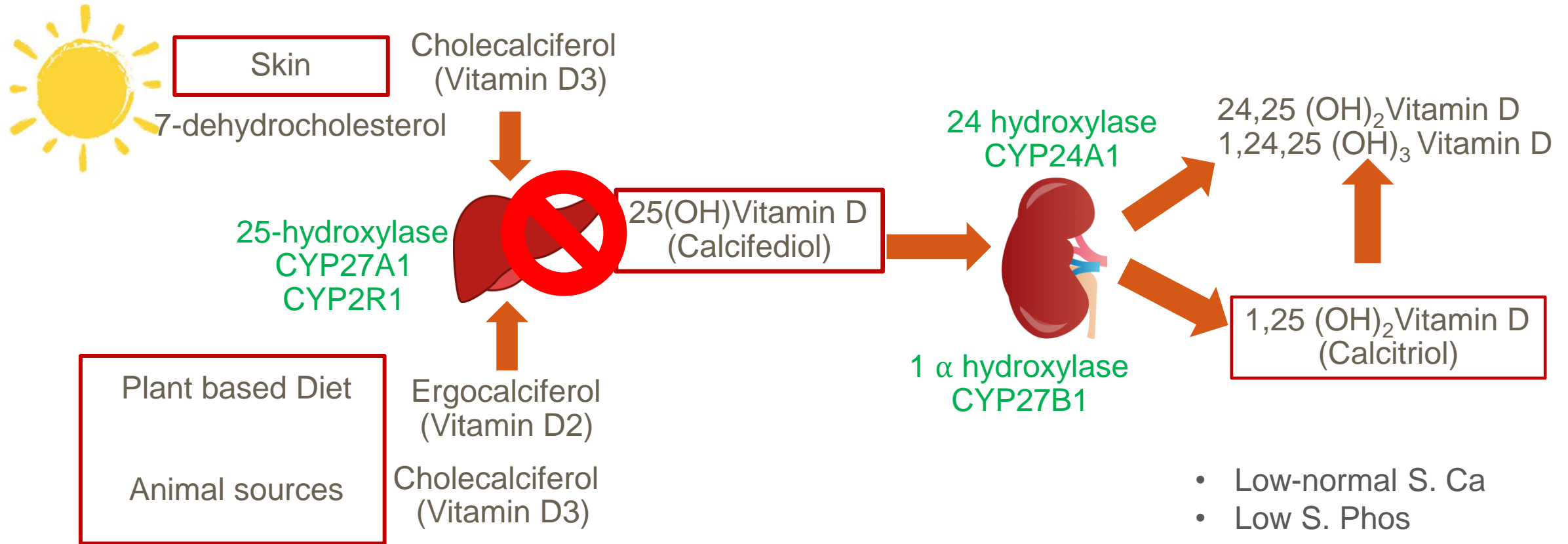
- IV Calcium (Seizures or acute EKG changes)
 - Oral calcium (Check elemental calcium)
 - Calcitriol (essential for hypoparathyroidism, PHP)
 - Don't forget to treat hypomagnesemia
 - Vitamin D supplementation
-
- Hypoparathyroidism: risk of nephrocalcinosis; goal low normal serum Ca
 - Pseudohypoparathyroidism: no hypercalciuria; goal normal Ca and PTH



Vitamin D Deficiency - Nutritional

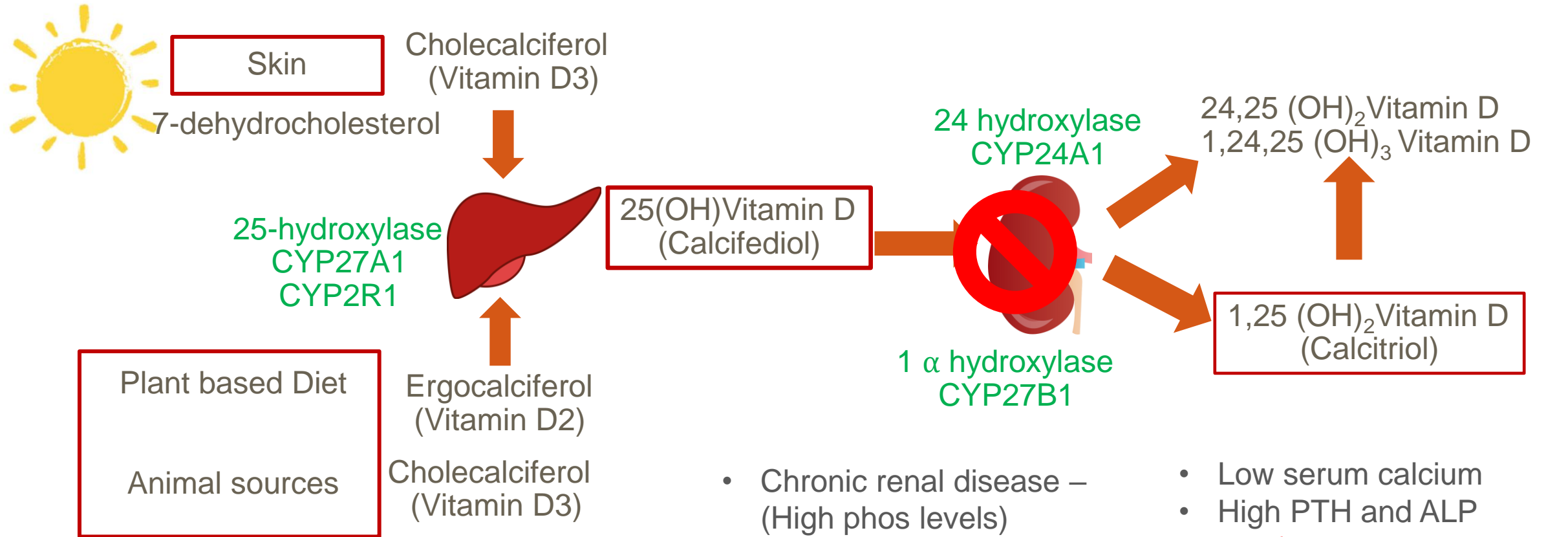


Vitamin D Deficiency - Gastrointestinal



- Low-normal S. Ca
- Low S. Phos
- High PTH
- High ALP
- Low 25-OHD

Vitamin D Deficiency - Renal



- Chronic renal disease – (High phos levels)
- Autosomal recessive 1 α hydroxylase deficiency (low phos level)

- Low serum calcium
- High PTH and ALP
- **Low/undetectable 1,25D**
- Normal 25-OHD

Vitamin D Receptor Resistance

- Mutations in the gene encoding vitamin D receptor (VDR)
- Labs:
 - Low serum calcium
 - Low serum phos
 - High PTH
 - **Very High 1,25 (OH)₂ Vitamin D**
 - Normal 25 (OH) Vitamin D
- Growth failure, rickets, bone pain, partial or complete **alopecia**





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Hypercalcemia



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Hypercalcemia - Symptoms

- Polyuria, polydipsia
- Anorexia, nausea and vomiting
- Failure to thrive in infants and toddlers
- Constipation
- Hypotonia
- Irritability/seizure/depression
- Renal calculi
- Bone pain
- Hypertension



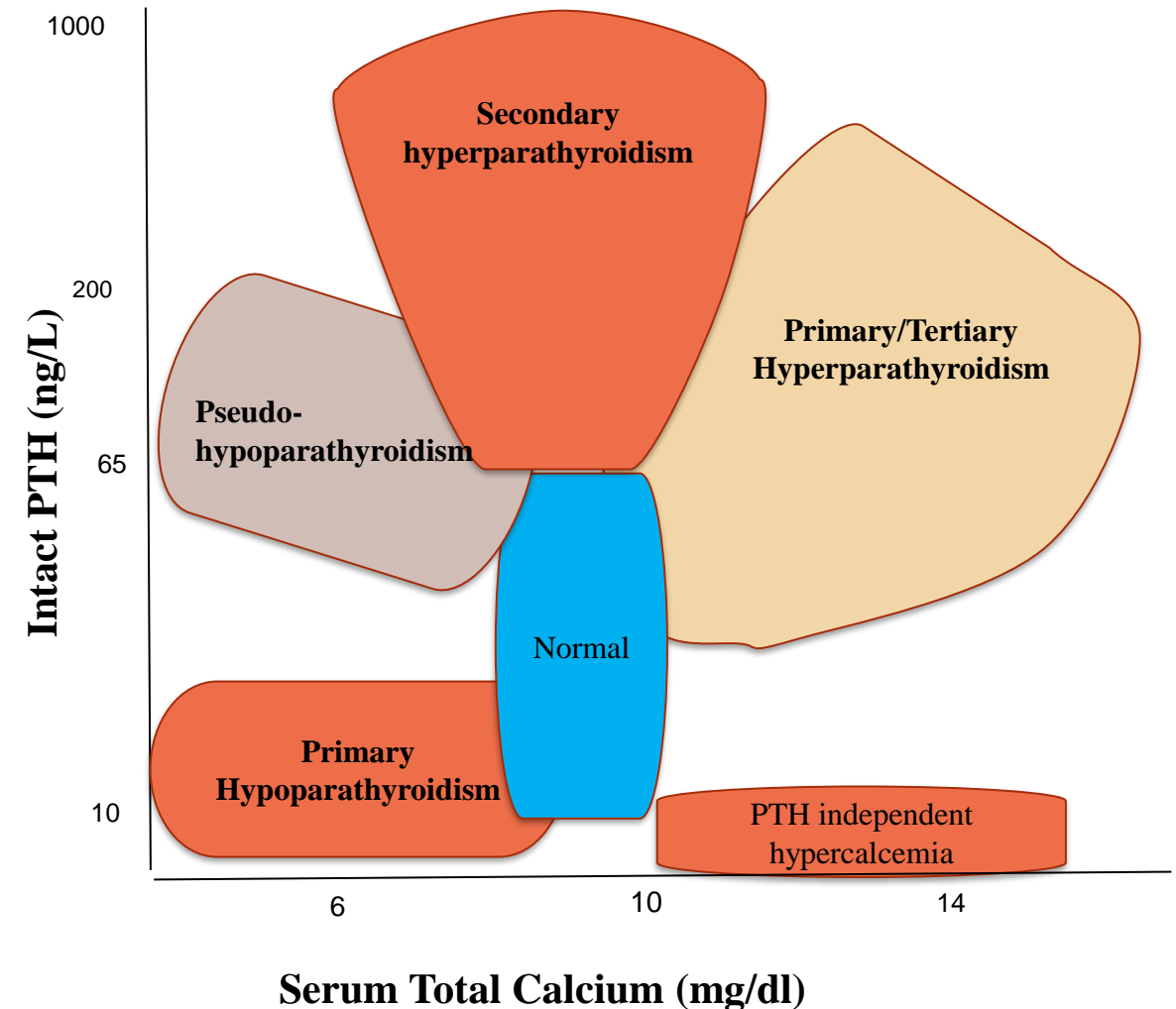
Hypercalcemia - Causes

- Excessive Intake
 - Calcium (for phosphorus binding)
 - Vitamin D intoxication
- Bone resorption
 - Hyperparathyroidism
 - Sporadic
 - Inherited (MEN I, IIA)
 - Hyperthyroidism
 - Vitamin A toxicity
 - Immobilization
 - Malignancy
- Renal reabsorption
 - Familial hypocalciuric hypercalcemia
 - Medications (thiazides)
- Others
 - Williams-Beuren Syndrome
 - Cocktail personality, elfin facies, supraaortic stenosis, developmental delay
 - Contiguous gene deletion (7q11.23), *ELN* gene
 - Hypercalcemia spontaneously resolves by age 1
 - Adrenal Insufficiency
 - Hypophosphatasia
 - Granulomatous & inflammatory diseases
 - Activated 1 α hydroxylase



Hypercalcemia - Evaluation

- Critical labs
 - Serum Calcium + albumin; iCa
 - Serum Phosphorus
 - Serum Creatinine
 - iPTH
 - Spot or 24-hour Urine Ca/Cr**
(can be elevated in hyperparathyroidism)
- 25 (OH) vitamin D
- 1,25 (OH)₂ vitamin D
- PTHrP, Vitamin A
- TFTs, Cortisol and ACTH



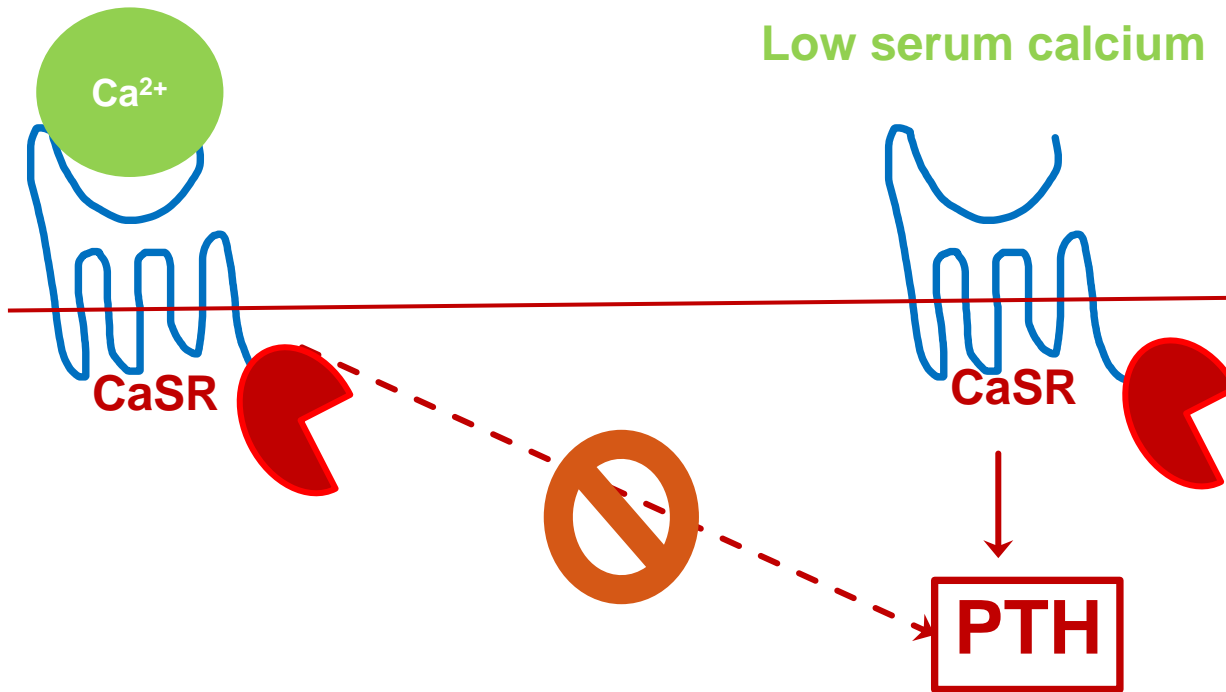
- Certain neoplasia can secrete high levels of PTHrP
 - binds to PTH/PTHrP receptor -> symptoms of hyperparathyroidism
- Osteolytic metastases with local release of cytokines (including osteoclast activating factors)
- Inflammatory macrophages/monocytes or neoplastic cells may express 1 α hydroxylase activity
 - excess 1,25 (OH)₂ Vitamin D



Familial Hypocalciuric Hypercalcemia (FHH) Neonatal Severe Hyperparathyroidism (NSHPT)



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- Inactivating mutation in *CaSR*, *GNA11*, *AP2S1* genes

- **FHH** - Heterozygous
 - “Benign” elevation in S. Ca levels
 - Mildly elevated S. Mg levels
 - S. Phos – low-normal
 - **Low urine Ca/Cr ratio**
 - Inappropriately normal PTH

- **NSHPT** - Homozygous
 - Elevated PTH and S. Ca levels
 - Low S. Phos level



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Hypercalcemia - Management

- **Acute**

- Hydration (normal saline)
- Loop diuretics— for fluid overload (not first line) – do not recommend prolonged use
- Oral phosphate for binding of calcium in intestine
- Calcitonin
- Dialysis

- **Long-term**

- Treat the underlying cause
- Bisphosphonates, *denosumab
- Glucocorticoids (inhibits 1 α hydroxylase activity) – decreases GI absorption of calcium
- Calcimimetic agents (Allosteric activators of CaSR-> reduce PTH secretion)
- Parathyroidectomy

Hungry Bone Syndrome

- Due to chronic increase in bone resorption
- Bone influx of minerals after acute drop in PTH levels due to continued increased osteoblastic activity
 - Severe hypocalcemia
 - Hypophosphatemia
 - Hypomagnesemia
 - Elevated alkaline phosphatase, osteocalcin, radioactive isotope uptake





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Hypophosphatemia



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Hypophosphatemia

- Symptoms:
 - Muscle weakness
 - Fatigue
 - Acute neurological symptoms – paresthesia, altered mental status, seizures
- Causes:
 - Renal phosphate wasting
 - Hyperparathyroidism (primary, tertiary)
 - Redistribution (refeeding syndrome)

FGF23 Independent Hypophosphatemia

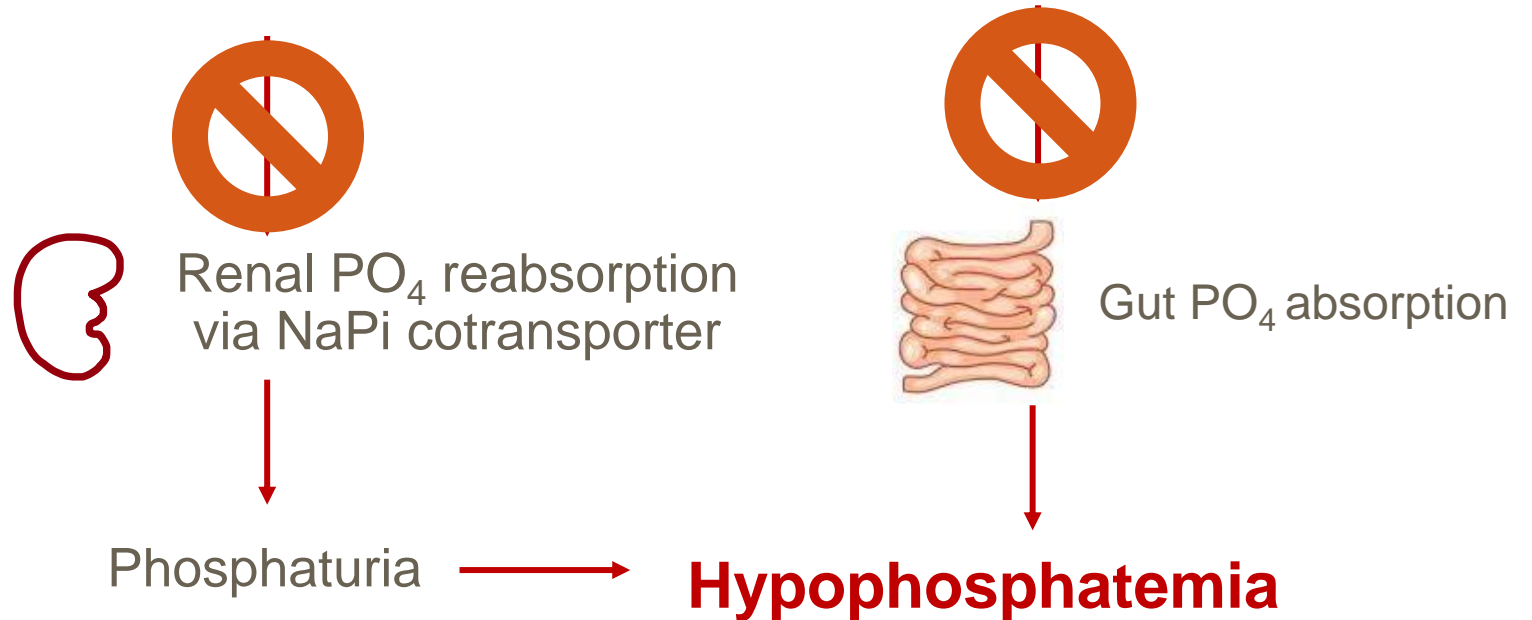
- Fanconi syndrome
 - Renal wasting of phosphorus, glucose, potassium, bicarbonate, uric acid, amino acids
 - Various diseases, medications, toxins
- HHRH (Hereditary Hypophosphatemic Rickets with Hypercalciuria)
 - *SLC34A3* gene mutation – encodes NaPi cotransporter
 - Normal-high serum calcium, **low serum phos**, normal PTH, normal 25 (OH) vitamin D, **high 1,25 (OH)₂ Vitamin D**, elevated urine Ca excretion
 - Kidney stones, rickets/osteomalacia
- Hyperparathyroidism

FGF23 Mediated Hypophosphatemia

PHEX, DMP1



- Low serum phos
- High urine phos
- Normal serum calcium
- Elevated ALP
- Normal 25 (OH) vitamin D
- Normal/low 1,25 (OH)₂ Vitamin D
- Normal/slightly increased PTH



FGF23 Mediated Hypophosphatemia

- Disorders of reduced inactivation
 - X-linked hypophosphatemic rickets (XLH)
 - *PHEX*
 - Autosomal dominant hypophosphatemic rickets (ADHR)
 - *FGF23* (at the cleavage site)
 - Autosomal recessive hypophosphatemic rickets (ARHR)
 - *DMP 1, ENPP1, FAM20C*
- Disorders of overproduction
 - Tumor induced rickets/osteomalacia (TIO) (Oncogenic osteomalacia)
 - From underlying mesenchymal tumor
 - McCune Albright syndrome
 - From fibrous dysplasia



Hypophosphatemia - Evaluation

- Fractional excretion of Phosphate (FEP)

$$\left[\frac{\text{Urinary Phosphate} \times \text{Serum creatinine}}{\text{Serum Phosphate} \times \text{Urinary creatinine}} \right] \times 100.$$

- TRP (Tubular reabsorption of Phosphorus) % = 1- FEP
- $$\text{TP/GFR} = \frac{\text{Serum Phosphate} - \text{Urine phosphate} \times \text{Serum Creatinine}}{\text{Urine Creatinine}}$$

Hypophosphatemia - Treatment

- Phosphorus supplements and calcitriol
 - Renal calcifications
 - Secondary hyperparathyroidism
- Burosumab (FGF23 monoclonal antibody)
 - Binds and blocks FGF23
 - Approved for treatment of XLH (>6 months of age), TIO
- Phosphorus supplements alone for HHRH





Hyperphosphatemia



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Hyperphosphatemia - Causes

- Acute phosphate load
 - Cell lysis (tumor lysis, rhabdomyolysis, crush injuries, hemolytic anemia)
 - Exogenous phosphate administration (Fleet enema, high phosphate formulas in neonates)
- Renal insufficiency
- Hypoparathyroidism
- Tumoral calcinosis



Tumoral Calcinosis

- Autosomal Recessive disorder due to inactivating mutations in
 - GALNT3 gene
 - FGF23 gene
 - Klotho gene
- Low FGF23 bioactivity leads to hyperphosphatemia
 - ↑calcitriol level -> hypercalcemia-> suppress PTH
 - Vascular and periarticular calcifications
 - Elevated inactive C terminal fragment of FGF23



Hyperphosphatemia - Treatment

- Treat underlying disease
- Manage hypocalcemia
- Low phosphorus diet
- Phosphate binding agents
- Dialysis



Disorders of Magnesium



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Hypomagnesemia

- Symptoms of hypocalcemia
 - Decreases PTH secretion and action
- Irritability
- Muscle twitches
- Jitteriness
- Tremors
- Poor feeding
- Lethargy
- Seizures



Hypomagnesemia - Causes

- **Primary:**
 - Autosomal recessive mutations in TRPM6 (Mg channel in intestine and kidney)
 - Gitelman and Bartter syndrome
 - Autosomal dominant hypocalcemia (activating mutation of CaSR)
 - Several other genetic mutations
- **Secondary:**
 - Intestinal losses - acute or chronic diarrhea, steatorrhea, or malabsorption, drugs (laxative, PPI)
 - Renal losses- diuretic use, nephrotoxins (such as aminoglycosides, amphotericin B), and renal tubular dysfunction or tubular-interstitial disease
 - Inadequate intake when TPN dependent
 - Shifts from intravascular space: “hungry bone syndrome” or refeeding syndrome



Hypermagnesemia

- Symptoms:
 - Mild: Asymptomatic
 - Rising levels: Flushing, nausea, headaches
 - Severe: hypoventilation, muscle paralysis, arrhythmia, respiratory arrest, asystole
- Causes:
 - Renal insufficiency
 - Excess intake
 - Tocolytic agent (maternal and fetal toxicity)
 - Enema, antacids, adjuvant treatment of moderate - severe asthma
- Also suppresses PTH secretion



Evaluation and Treatment

- FEMg (urine Mg x serum Cr/urine Cr x Serum Mg) x 100
 - If <2%, likely extrarenal losses
- Hypomagnesemia
 - Seizures: IV bolus 2.5-5 mg/kg of 50% magnesium sulfate with EKG monitoring
 - Magnesium supplements (high oral doses can cause diarrhea)
 - Hypocalcemia can be refractory to therapy until Magnesium given
- Hypermagnesemia
 - Remove the source
 - Hydration, loop diuretics, dialysis
 - Hemodynamic, respiratory support
 - Calcium and calcitriol supplementation





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Bone Physiology



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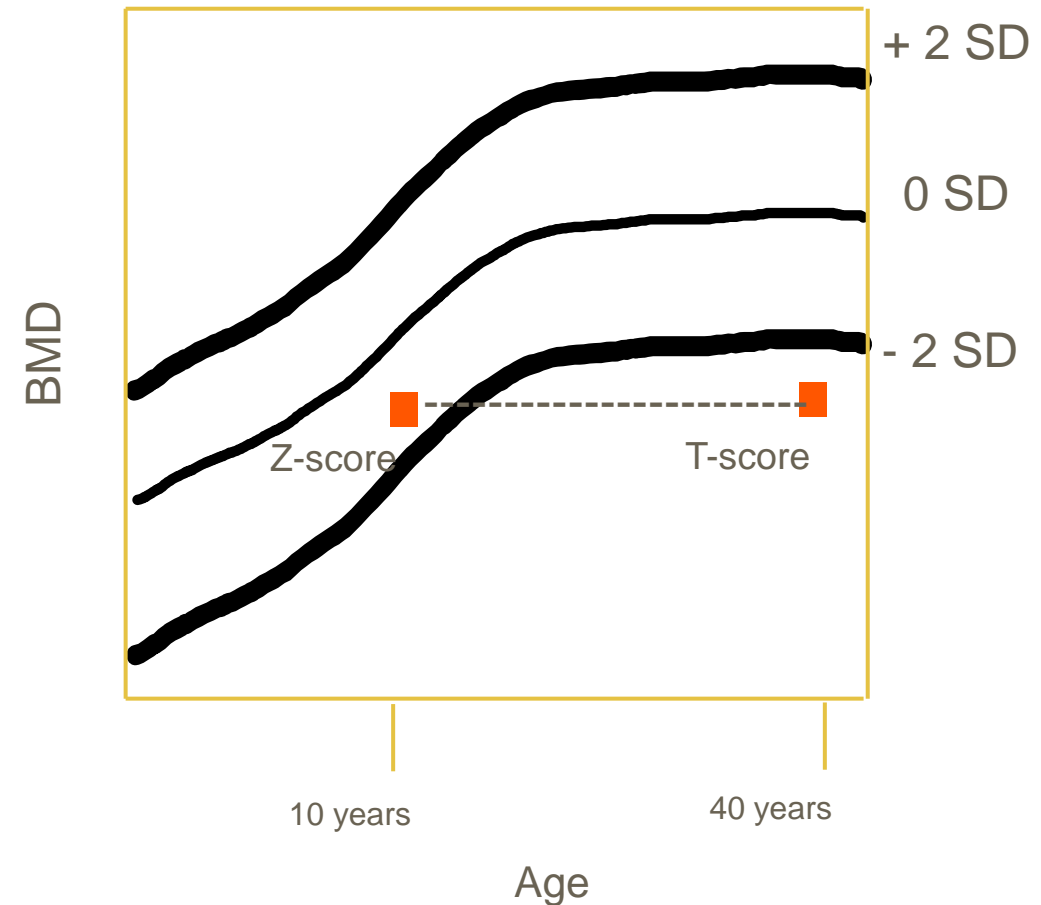
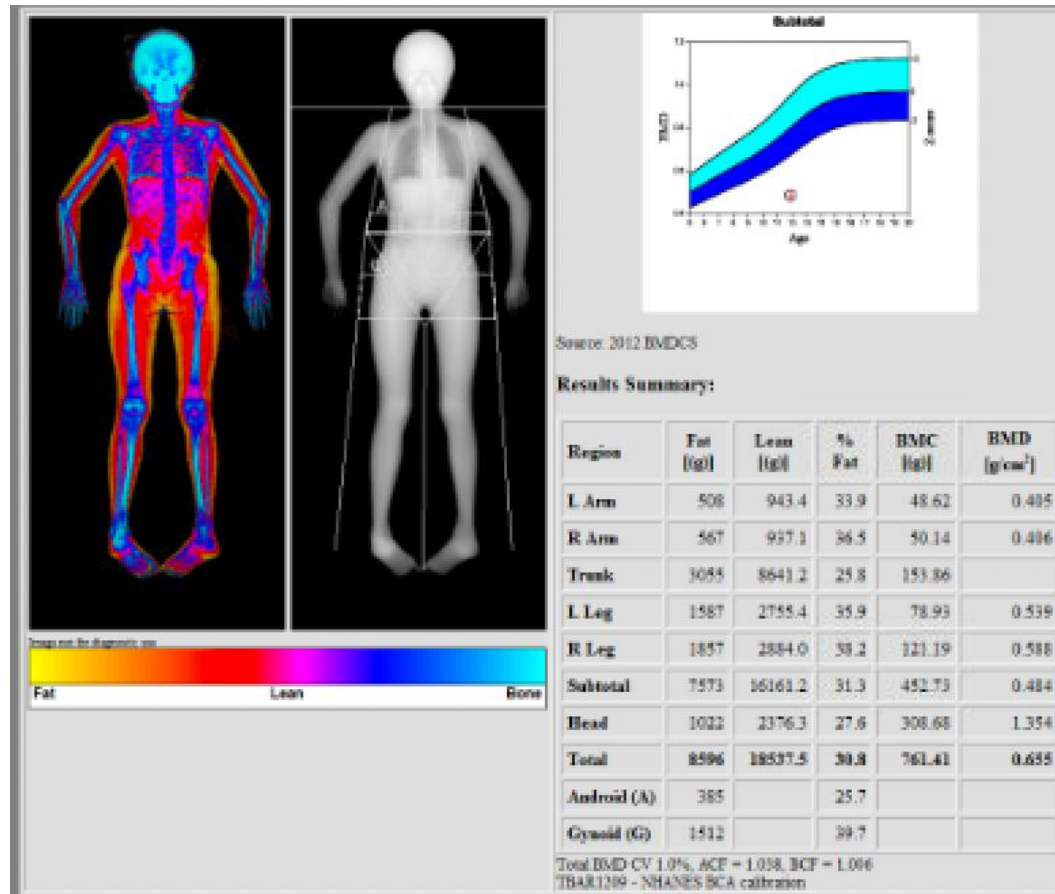
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Bone Density Measurement Techniques

- Plain radiograph – very insensitive
- Quantitative CT – vBMD
 - Peripheral vs central
 - Distinguish trabecular vs cortical bone
 - Radiation, inability to reliably measure the same site in a growing child
- DXA (Dual energy X ray absorptiometry) - aBMD
 - Low radiation – 2 radiation beams to distinguish bone from soft tissue
 - Short scan time
 - Good reproducibility
 - Appropriate positioning, different body sites
 - Comparison – same scanner; Pediatric software



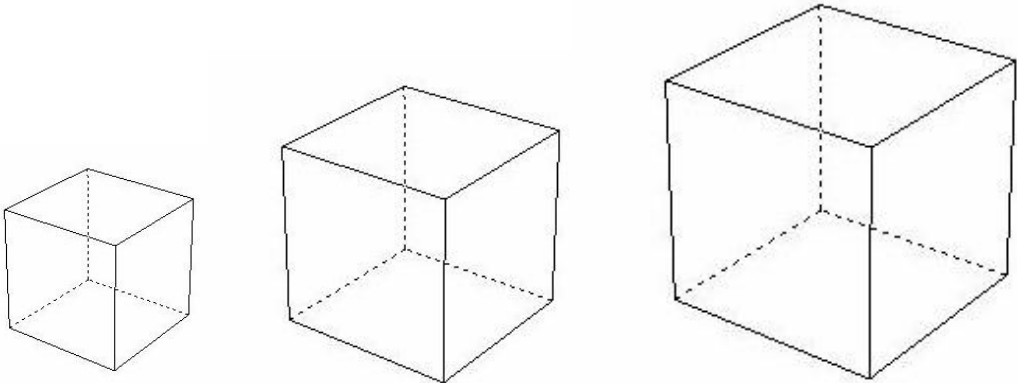
DXA – Use the Z-score



Z-score = SD from mean for age, sex, ethnicity
T score = SD score compared to young adults who have attained peak bone mass

Bone Density affected by Stature and Puberty

Adjust for height and maturity



	1 cm	2 cm	3 cm
BMC (g)	1	8	27
Area (cm ²)	1	4	9
aBMD (g/cm ²)	1	2	3
vBMD (g/cm ³)	1	1	1

Overestimated in Tall Stature
Underestimated in Short Stature



Bone Disorders



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Rickets and Osteomalacia

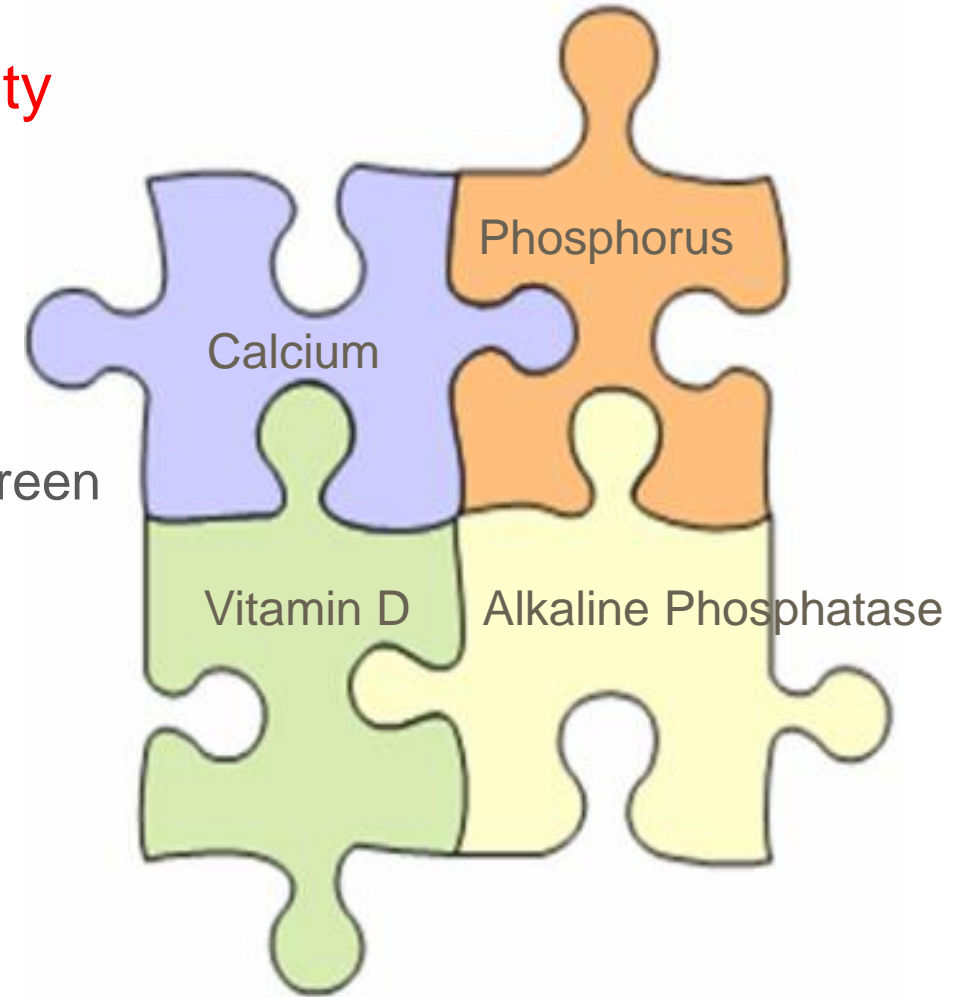
- Rickets: Defective mineralization of the growth plates
- Osteomalacia: Defective mineralization of cortical and trabecular bone surfaces
- Symptoms
 - Bone pain, anorexia, failure to thrive, gross motor delay
 - Symptoms of hypocalcemia (rarely)
- Signs
 - Flaring, fraying, and cupping of metaphysis and epiphysis
 - Caput quadratum
 - Delayed closure of fontanelles
 - Rachitic rosary
 - Genu varus or genu valgum
 - Poor growth



Rickets and Osteomalacia

- Calcium deficiency**
- Phosphorus deficiency**
- Vitamin D deficiency or resistance
 - Nutritional, maternal deficiency, exclusive breast feeding
 - Inadequate exposure to sun, high melanin content, sunscreen
 - Malabsorption
 - Liver or renal disease
 - VDR mutations
 - Obesity
 - Increase catabolism (like anticonvulsants)
- Hypophosphatasia

** TPN, prematurity



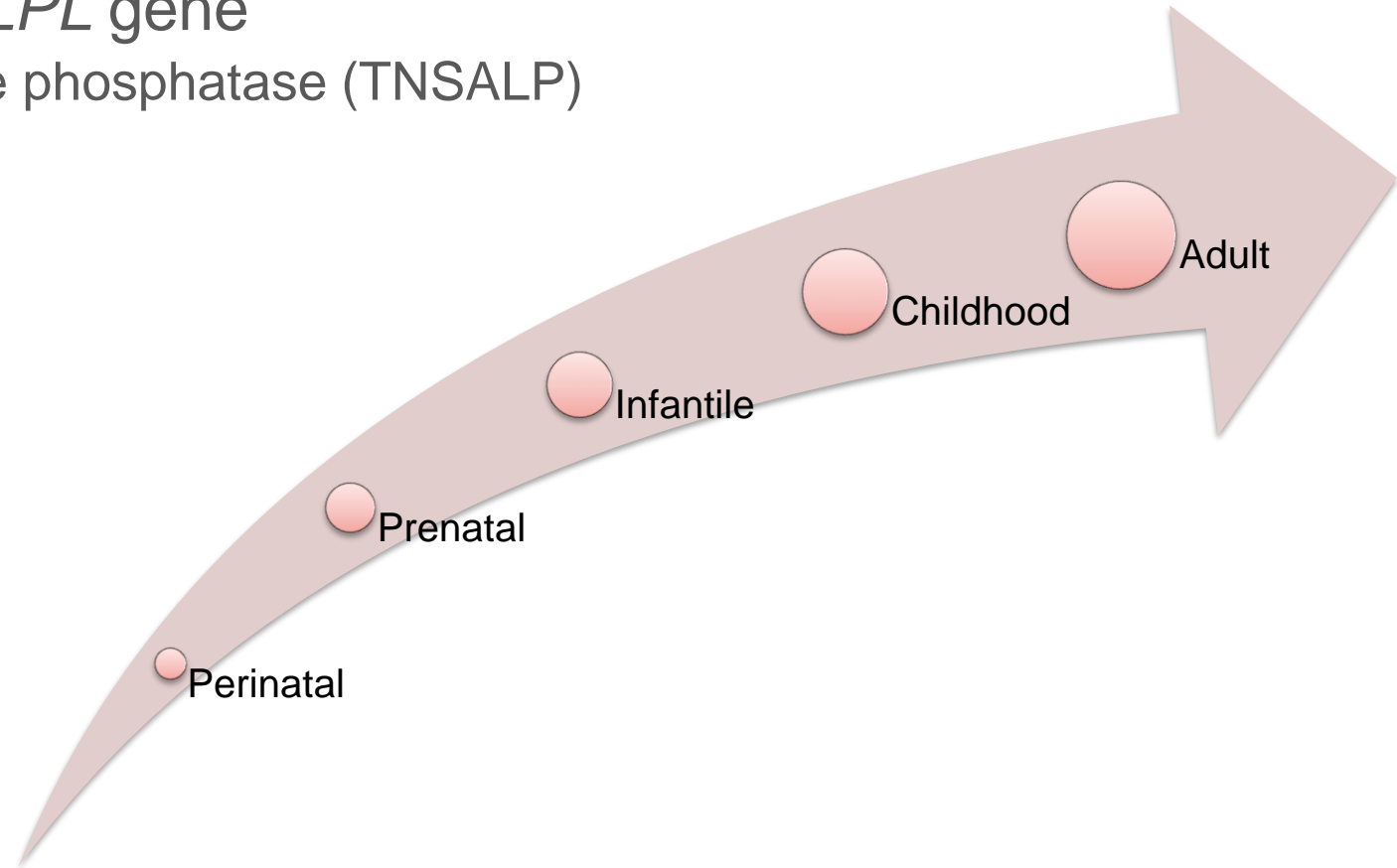
Metabolic Bone Disease of Prematurity

- Rickets or osteopenia of prematurity
 - Can present with bone fragility
- Multifactorial:
 - Prematurity (Failure to accrue bone mineral in third trimester)
 - Chronic medical problems; Medications used to treat them
 - Inadequate intake of minerals post birth, TPN dependency, aluminum toxicity
- Management:
 - Supplemental minerals +/- calcitriol



Hypophosphatasia

- Loss of function mutations in the *ALPL* gene
 - Deficiency of tissue nonspecific alkaline phosphatase (TNSALP)
 - Autosomal recessive or dominant
 - Undermineralized bone and teeth
- Spectrum of phenotype
 - Mildest – Odontohypophosphatasia
 - Bone and joint pain
 - Stress fractures
 - Craniosynostosis
 - Seizures
 - Early deciduous teeth loss (root intact)



Hypophosphatasia

- Lab Evaluation:
 - Low ALP (age dependent range!)
 - Accumulation of phosphoethanolamine (PEA), pyridoxal 5'-phosphate (PLP), and inorganic pyrophosphate (PPI)
 - Hypercalcemia, hypercalciuria
- Treatment:
 - Enzyme (asfotase alfa) replacement (subcutaneous injections)
 - Supportive management
 - Team approach (dentist, orthopedics, physical therapist, neurosurgery, pain management)
 - Vitamin B6 for seizures
 - Management of hypercalcemia
 - Avoid bisphosphonates



Pediatric Osteoporosis is a **Clinical** Diagnosis

- Clinically significant fracture history
 - One or more non traumatic vertebral compression fracture
- OR
- Low BMC/BMD (Z-score < -2*) & **long bone** fractures
 - 2 or more by age 10**
 - 3 or more by age 19

*BMD as a spectrum

**Integrating fracture characteristics and clinical context into diagnostic approach

Gordon CM. *J Clin Densitometry* 2014 Apr-Jun;17(2):219-24

Osteoporosis

- Primary:
 - Juvenile osteoporosis (IJO or mutations in *WNT*, *LRP5*, *PLS3*)
 - Connective tissue disorders: Osteogenesis Imperfecta, Marfan syndrome, EDS, Bruck syndrome, homocystinuria
- Secondary:
 - Immobilization: Cerebral Palsy, muscular dystrophies
 - Chronic disease: Cystic Fibrosis, IBD, malignancy, rheumatologic, transplantation, eating disorders etc.
 - Endocrine disease: Hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing syndrome, growth hormone deficiency
 - Bone toxic medications: Glucocorticoids, depot provera, antiepileptics etc.



Idiopathic Juvenile Osteoporosis (IJO)

- Rare form of primary osteoporosis
- Symptoms:
 - Presents in prepubertal period in a previously healthy child
 - Bone fragility (VF, sub-metaphyseal fractures of long bones)
 - Proximal muscle weakness and back/hip pain
- Signs:
 - Lack features of Osteogenesis Imperfecta
 - Osteopenia, fractures, radiolucent bands at metaphyses of long bones
- Etiology:
 - Unclear; some have heterozygous mutations of *LRP5*
 - Reduced bone formation based on histomorphometry
- Resolves spontaneously after puberty



Osteogenesis Imperfecta (OI)

- Heterogenous group of connective tissue disorders
- Bone fragility, low bone mass
- Extra-skeletal features:
 - Blue-grey sclera
 - Skin laxity
 - Hearing loss
 - Joint hyperextensibility
 - Short stature
 - Dentinogenesis imperfecta
 - Cardiovascular, respiratory, neurological manifestations



Osteogenesis Imperfecta (OI)

- Etiology
 - Majority – autosomal dominant mutations in *Col1A1*, *Col1A2* (encode collagen I)
 - Autosomal recessive
 - X Linked recessive
- Broad spectrum of clinical presentation; Sillence classification
 - Type 1 (mild)
 - Type 2 (perinatal lethal)
 - Type 3 (severe)
 - Type 4 (moderate)

Management of Pediatric Osteoporosis

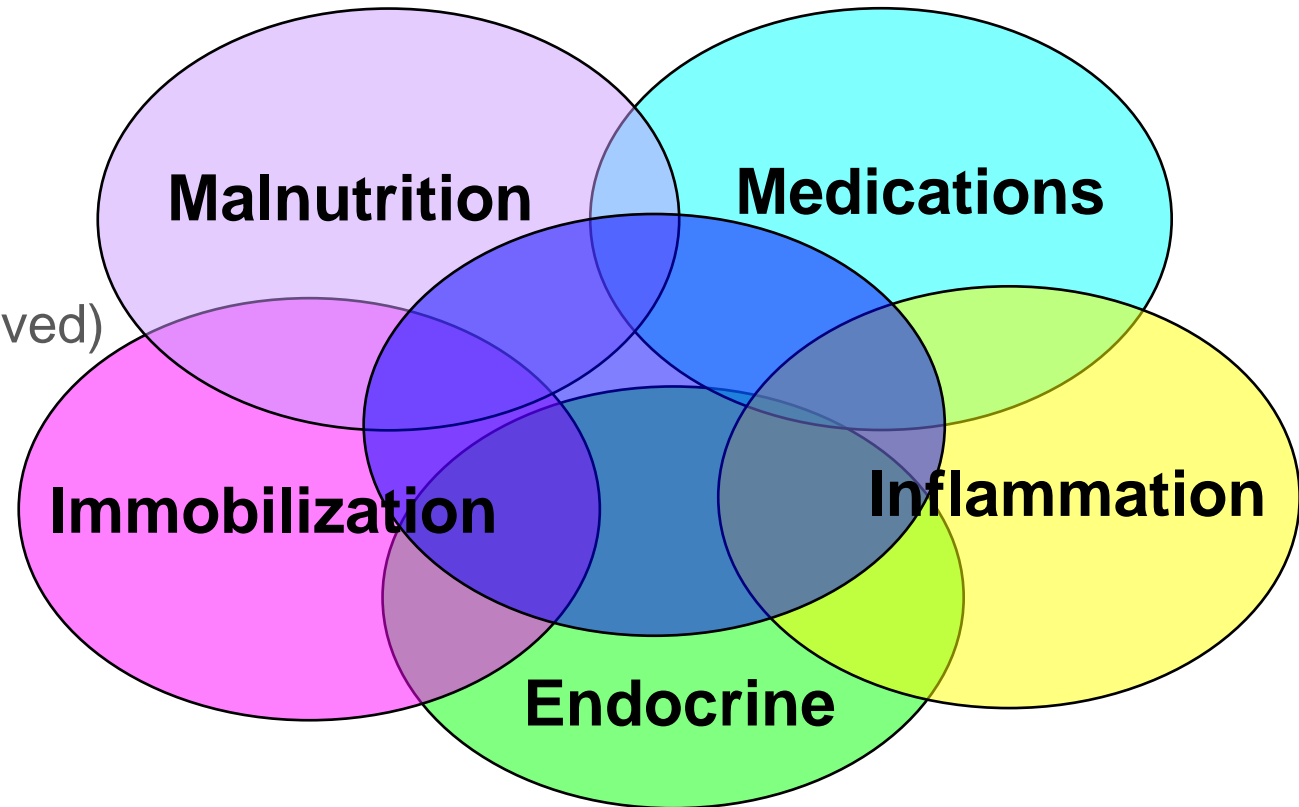
- Pharmacologic therapy:

- Anabolic

- Growth Hormone
 - PTH (black box warning – recently removed)
 - Anti Sclerostin antibody*

- Antiresorptive

- Sex steroids
 - Bisphosphonates
 - RANK-L blocking antibody*



Bisphosphonates

- Synthetic pyrophosphate analogues
 - Binds to hydroxyapatite crystals
 - Inhibits osteoclast mediated bone resorption
- Increase BMC/BMD, reshape vertebral bodies, increase cortical thickness
- Pediatric uses:
 - Primary Osteoporosis (IJO and OI)
 - Secondary Osteoporosis except eating disorders
 - Hypercalcemia
 - Fibrous Dysplasia



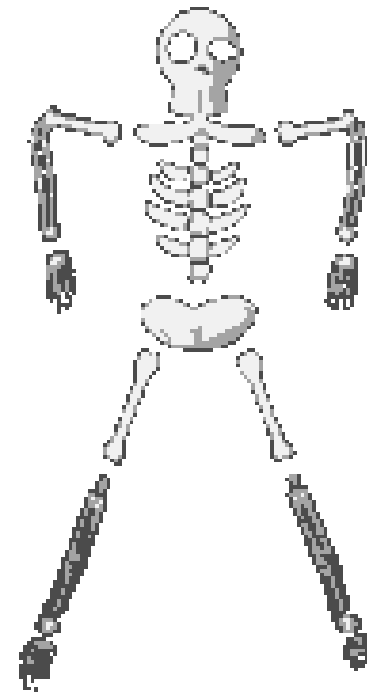
Osteopetrosis

- Rare disorder of defective bone resorption (osteoclasts)
- Symptoms:
 - Increased bone density, altered architecture, bone fragility
 - Narrow bone marrow space – pancytopenia, extramedullary hematopoiesis (HSM)
 - Compression of cranial nerves
 - Hypocalcemia - seizures
- Genetics:
 - Autosomal Dominant (mild), Autosomal recessive (malignant infantile), intermediate, X linked recessive (extremely rare)
- Management:
 - Only treatment for malignant infantile form is hematopoietic stem cell transplantation
 - Supportive management including calcium, vitamin D supplements





Supplemental material in handout



Audience Response Question 1

A 2.5-year-old female presents to your clinic with progressive bowing of legs. She was born full term and has no significant past medical or family history. She is taking vitamin D 600 IU daily supplements as recommended by her pediatrician. Radiographs demonstrate rickets. Her lab evaluation showed:

Serum calcium 9.5 mg/dl, Serum phosphorus 2.5 mg/dl, Serum magnesium 2 mg/dl
iPTH 37 pg/ml, ALP 700 U/L
25 (OH) Vitamin D 35 ng/ml, 1,25 (OH)₂ Vitamin D 145 pg/ml

Of the following, she most likely has a mutation in which gene:

- A. PHEX*
- B. DMP1*
- C. SLC34A3*
- D. FGF23*

Answer

C. *SLC34A3*

Hypophosphatemic **rickets** with hypercalciuria

Serum calcium 9.5 mg/dl, iPTH 37 pg/ml, **ALP 700 U/L**

Serum phosphorus 2.5 mg/dl, Serum magnesium 2 mg/dl

25 (OH) Vitamin D 35 ng/ml

1,25 (OH)₂ Vitamin D 145 pg/ml

Audience Response Question 2

A 4-year-old male presents to emergency room with seizures. He also had seizures last week at an outside hospital which were thought to be febrile seizures. Vitals stable and exam was unremarkable. Height 55%tile, weight 75%tile. Lab evaluation showed:

Serum calcium 4.1 mg/dl, albumin 4.3 mg/dl

Serum phosphorus 9 mg/dl, Serum magnesium 2 mg/dl

iPTH 250 pg/ml, ALP 200 U/L

25(OH)Vitamin D 30 ng/ml

What is the most likely defect associated with this condition?

- A. Autosomal dominant mutation
- B. Autosomal recessive mutation
- C. X linked recessive mutation
- D. Imprinting defect

D. Imprinting defect

Based on lab findings of hypocalcemia, hyperphosphatemia, elevated PTH the most likely diagnosis is pseudohypoparathyroidism. No features of Albright hereditary osteodystrophy on examination.

PHP Ib (epigenetic GNAS1 imprinting defect)

or

PHP II (some have PRKAR1A mutations)



Audience Response Question 3

A 15-year-old boy with Duchenne muscular dystrophy presents to clinic with acute onset back pain. He has been on glucocorticoids since age 8. He has never had any long bone fractures. He is slightly obese, sitting in wheelchair, has calf muscle hypertrophy, and is prepubertal. He has lower thoracic spine tenderness. Radiograph shows vertebral compression fractures from T10-L1. Lab evaluation showed:

Serum Calcium 9.1 mg/dl, albumin 4 mg/dl

Serum Phosphorus 4.5 mg/dl, Serum Magnesium 2 mg/dl

iPTH 30 pg/ml, ALP 80 U/L

25 (OH) vitamin D of 45 ng/ml

What are the factors contributing to secondary osteoporosis?

- A. Muscle dystrophy (inflammation)
- B. Chronic glucocorticoid therapy
- C. Immobilization
- D. Hypogonadism
- E. All of the above

Answer

E. All of the above

Key points:

Low bone turnover state with low bone formation rate

Secondary osteoporosis can be multifactorial

Treatment should address all the factors affecting bone health

Audience Response Question 4

A 2.5-year-old female presents to your clinic with progressive bowing of legs. She was born full term and has no significant past medical or family history.

On physical examination, her height is at the 2nd percentile and her weight is at the 45th percentile for age. She has thin eyelashes and patchy hair on her scalp. Rachitic rosary is noted at the chest wall and both wrists and ankles are widened. There is bilateral genu varum.

Radiographs demonstrate rickets.

Options

Of the following the lab findings most likely to be found in this patient:

	S. Calcium (mg/dl)	S. Phosphorus (mg/dl)	Alkaline Phosphatase (IU/L)	25 OH D (ng/ml)	1,25 (OH) ₂ D (pg/ml)
A.	8	3.5	450	22	321
B.	7.5	4.5	388	32	60
C.	9.8	4.5	100	25	25
D.	9.5	2.5	420	30	108

Answer

A. Very elevated $1,25(\text{OH})_2\text{D}$ level

Key points:

Growth failure, rickets, bone pain, partial or complete **alopecia**
End organ resistance -> VDR mutation

Audience Response Question 5

- A 2-year-old boy presents to PCP's office for a viral illness. Subsequent lab evaluation is within normal limits except an elevated alkaline phosphatase level of 1400 IU/L.
- PCP asks for patient to return for a more thorough examination and does not find any signs/symptoms of liver disease or rickets.
- 4 weeks after this visit, repeat labs are done which show serum alkaline phosphatase level of 650 IU/L.



What is the next best step in management of this patient?

- A. Treat with calcium and vitamin D
- B. Order a GGT level
- C. Order a skeletal survey to look for occult fracture
- D. Repeat alkaline phosphatase level in 2-3 months

D. Repeat alkaline phosphatase level in 2-3 months

Key points:

Transient benign hyperphosphatasemia of infancy and childhood is not completely understood but could result in elevation of alkaline phosphatase after a viral illness or so. It usually self resolves within a few weeks to months.